Rates of Thrombus Events in Blood Contacting Medical Devices

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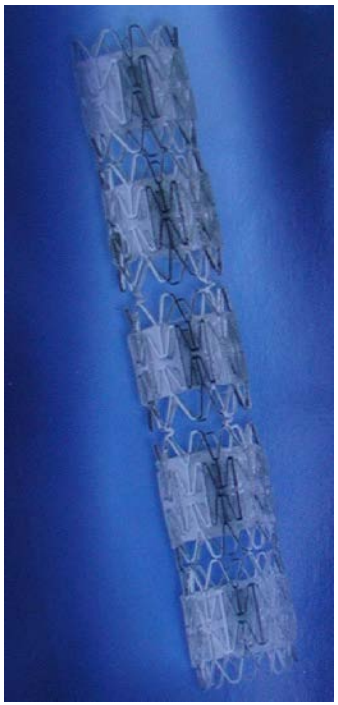
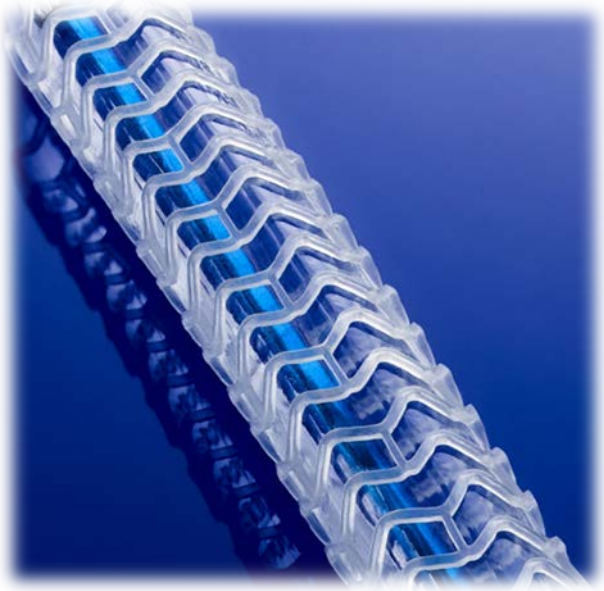
Is Thrombosis still a Relevant Concern in Blood Contacting Medical Devices?

- A search of thrombus related events reported to FDA was done through the MAUDE database
- A literature search was conducted
- Both searches focused on these device areas:
  - Stents
  - Grafts
  - Catheters
  - Hemodialysis
  - Bypass/Extracorporeal Membrane Oxygenation (ECMO)
  - Ventricular Assist Devices (VADs)

Stents



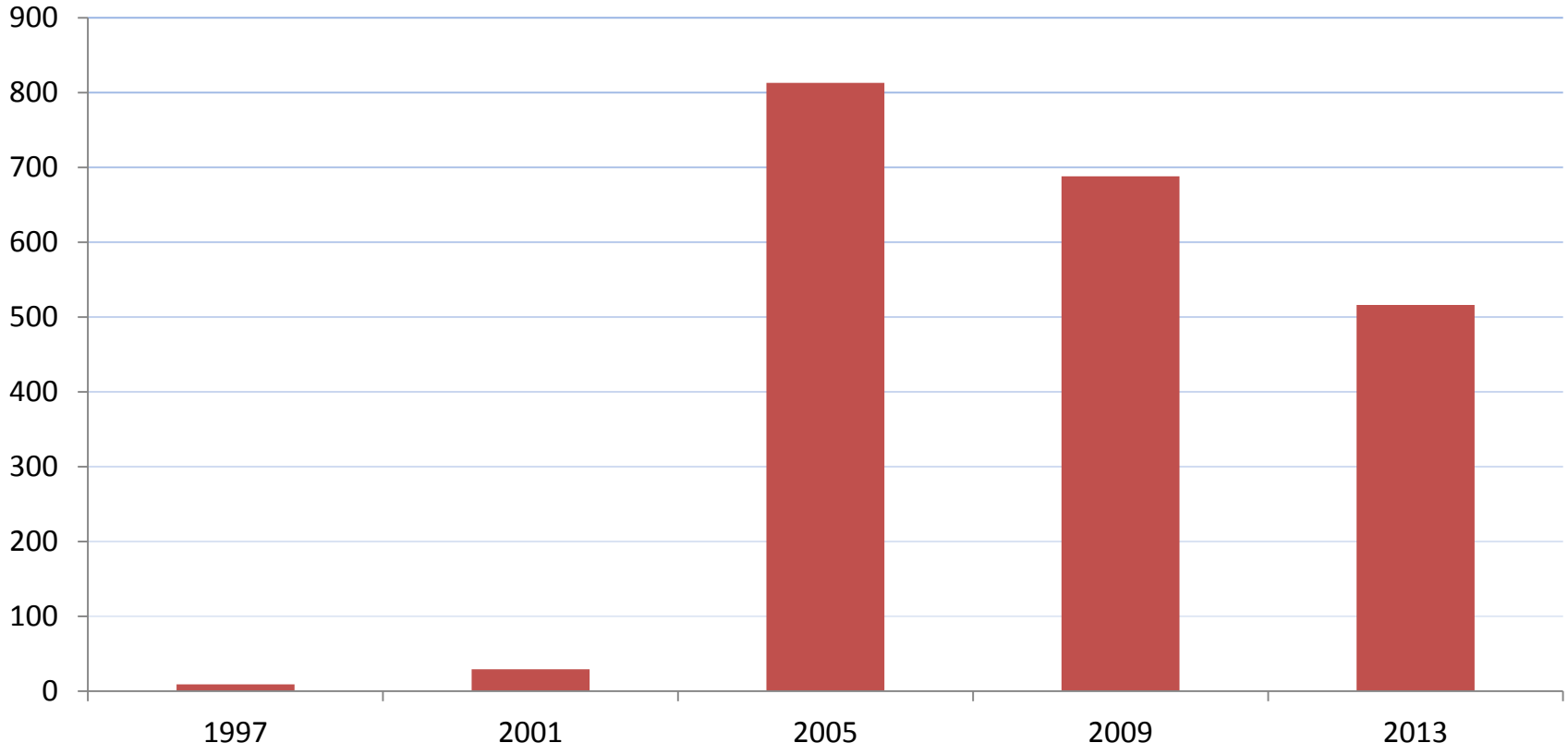


Bare Metal

Drug Eluting

Bioresorbable

Reported Thrombus Related Adverse Events for Stents

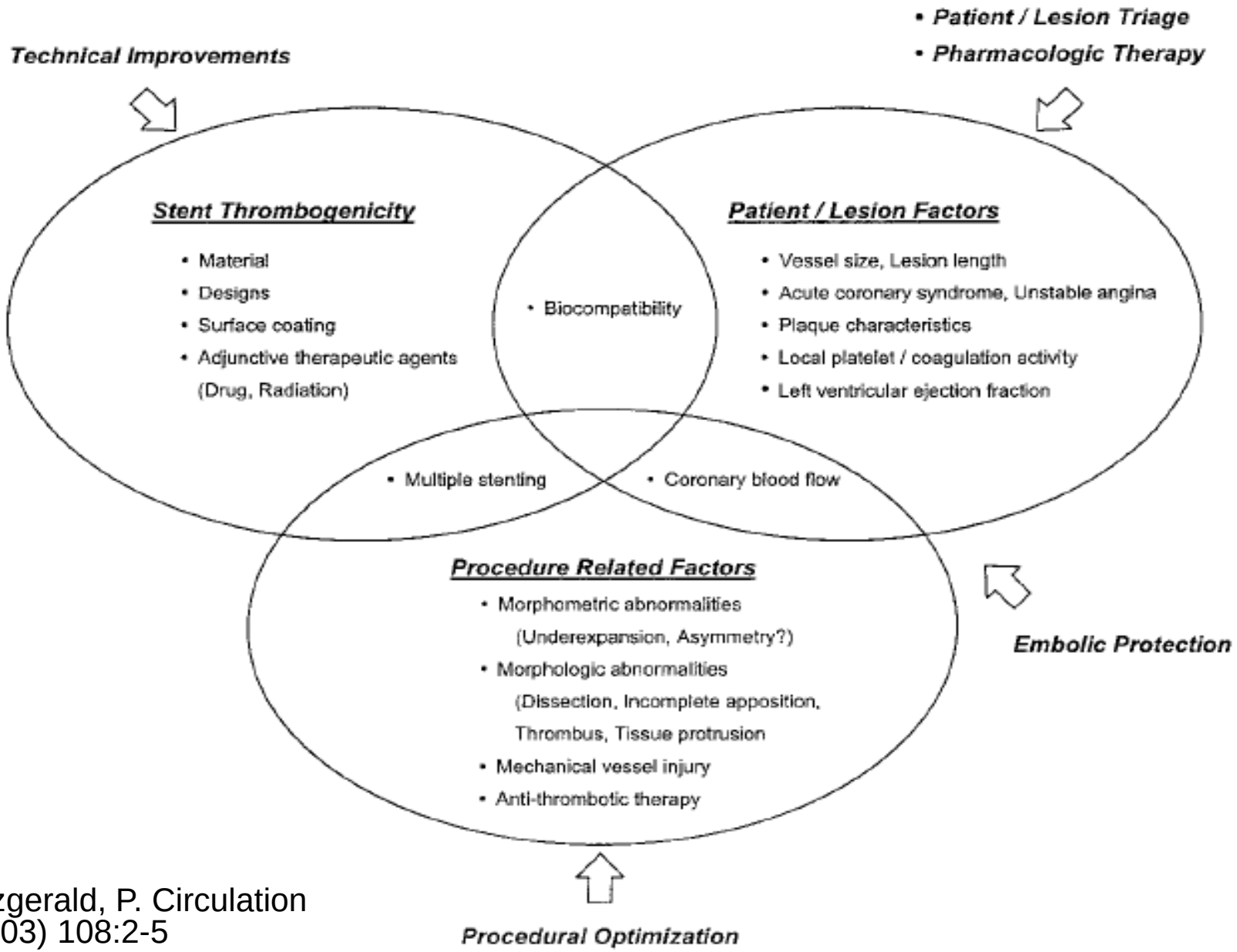


Data from FDA's MAUDE database

Literature Review Results for Stent Thrombus

- The number of stents implanted annually decreased slightly after 2006
  - currently 650-700,000 stents implanted/year
- Stent thrombosis now occurs in only 1-2% of patients
- Adverse effects are still myocardial infarction and/or death in > 70% of these patients

Wilson, WM, Cruden, NLM. (2013) 4:85-96



Fitzgerald, P. Circulation (2003) 108:2-5

Literature on Preclinical Test Methods for Stents

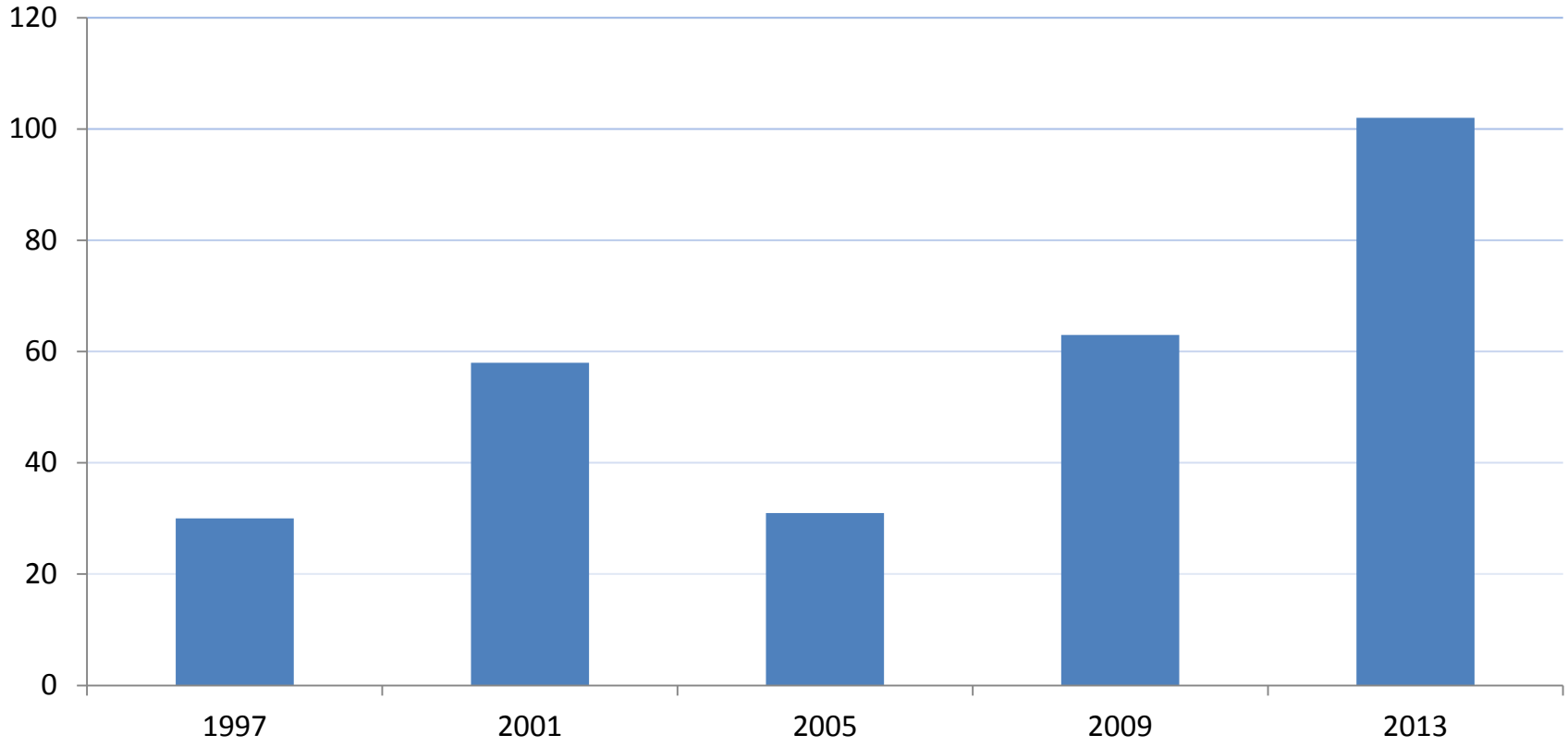
- Chandler-Loop or flow chamber models used
- Coagulation and inflammatory activation markers were measured in first study
  - TAT, β-TG, sP-selectin, SC5b-9 and PMN-elastase
- Platelet activation was tested for in second study
  - P-selectin, glycoprotein IIb/IIIa, PMC formation, SEM
- Statistically significant differences were found between the stent types

1. Scheuermann, S, et al. J Mater Sci Mater Med. (2011) 22(6):1521-1528.
2. Granada J, et al. J Thromb Thrombolysis (2010) 29:60-69

Endovascular Stent Grafts

SOURCE: Lombard Medical

Reported Thrombus Related Adverse Events for Endovascular Grafts



Data from FDA's MAUDE database

Literature Review Results for Endovascular Grafts

- 65-88% of aortic repair procedures performed in the US are now done using endovascular grafts, vs. 56% in 2009[1]
- Thrombus formation or embolization into aortic side branches often leads to ischemia
  - Typical ischemic complication rate is 3-10%[2]
- Thrombus has been linked to endoleaks and stent-graft migration[3]

1. Thompson, M. Medtech Insight (2013)
2. Maldonado et al, Vasc and Endovasc Surg (2007) 40:192-199
3. Sampaio, SM, et al. Annals of vascular surgery (2005) 19:1–8

Impact of Device Design on Endovascular Graft Thrombosis

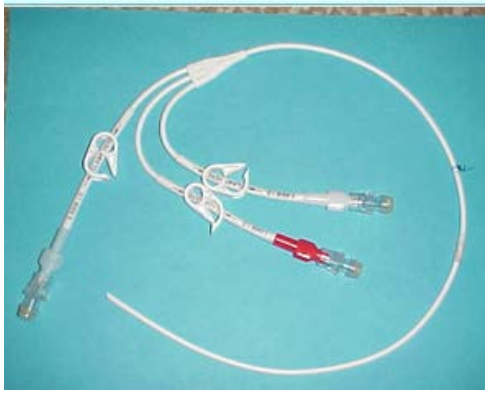
- In published results of the clinical study for the Aptus stent-graft device, thrombus-related events occurred in 34.8% of patients

- Root cause was found to be a manufacturing defect that caused shear stress induced platelet aggregation

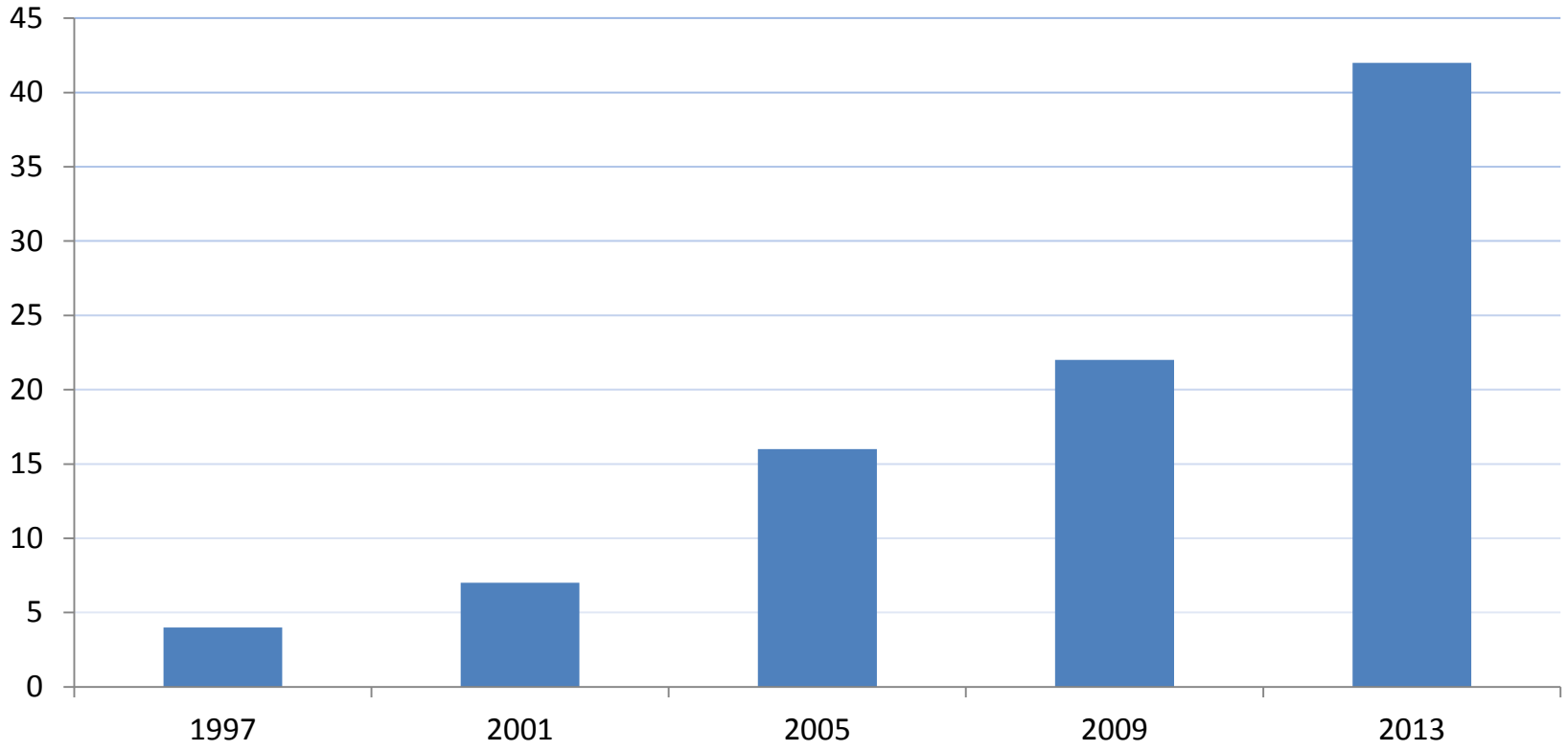
Mehta et al, J Vasc Surg (2012) 55(2):624

Catheters

- Search included several different types of catheters including:
  - Percutaneous
  - Angioplasty
  - Central venous
  - Cardiopulmonary bypass
  - Steerable
  - Introducers
  - Guidewire
  - Embolectomy
  - Continuous flush



Reported Thrombus Related Events for Catheters



Data from FDA's MAUDE database

Cardiac Catheterization – Literature Search Results

- Data on catheter related thrombus formation is very limited, and the true incidence is unknown
  - Thrombi are often stripped off when catheters are withdrawn
- An early clinical study showed thrombus formation on the catheter surface in 50% of patients undergoing diagnostic angiography[1]
- High shear stress occurs on the external surface of a catheter in the arterial system and this is known to cause platelet activation[2]

1. Formanek G., et al. Circulation (1970) 41:833-839
2. Chan, MY, et al. J Thromb Thrombolysis (2009) 28:366-380

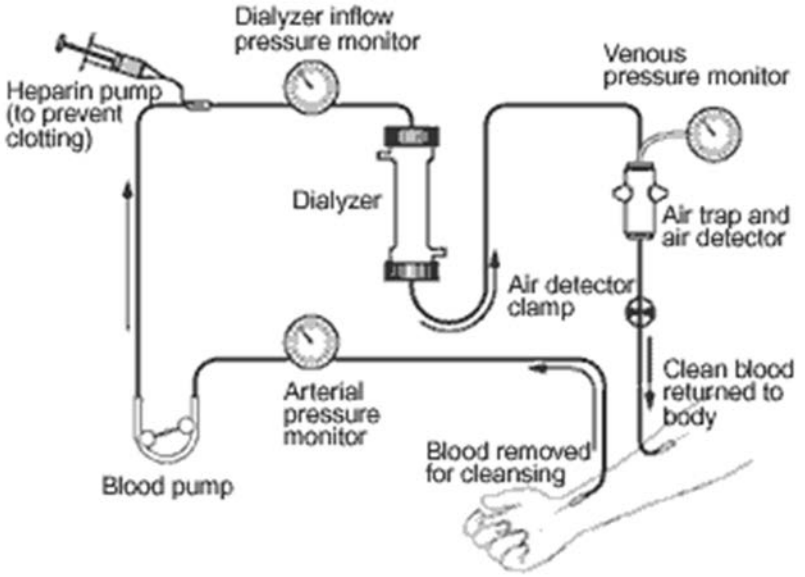
Central Venous Catheters – Literature Search Results

- Thrombosis is thought to be the precipitating event in 30-40% of central venous catheter malfunctions.[1]
- Use in infants and neonates has caused serious complications and is the main cause of thrombosis in this age group
- Peripherally inserted central catheters can lead to upper extremity deep vein thrombosis or pulmonary embolism[2]
- Dual lumen catheters are more likely to lead to total vessel occlusion[3]

1. Vascular Access 2006 Work Group. Am J Kidney Dis (2006) 48:S176-S247
2. Lobo, BL, et al. J Hosp Med (2009) 4(7):417-422
3. Haire, WD, et al. Bone Marrow Transplant. 1991 Jan;7(1):57-9.

Reported Thrombus Related Adverse Events for Hemodialysis Devices

- MAUDE search revealed only 1-2 reported events per time point

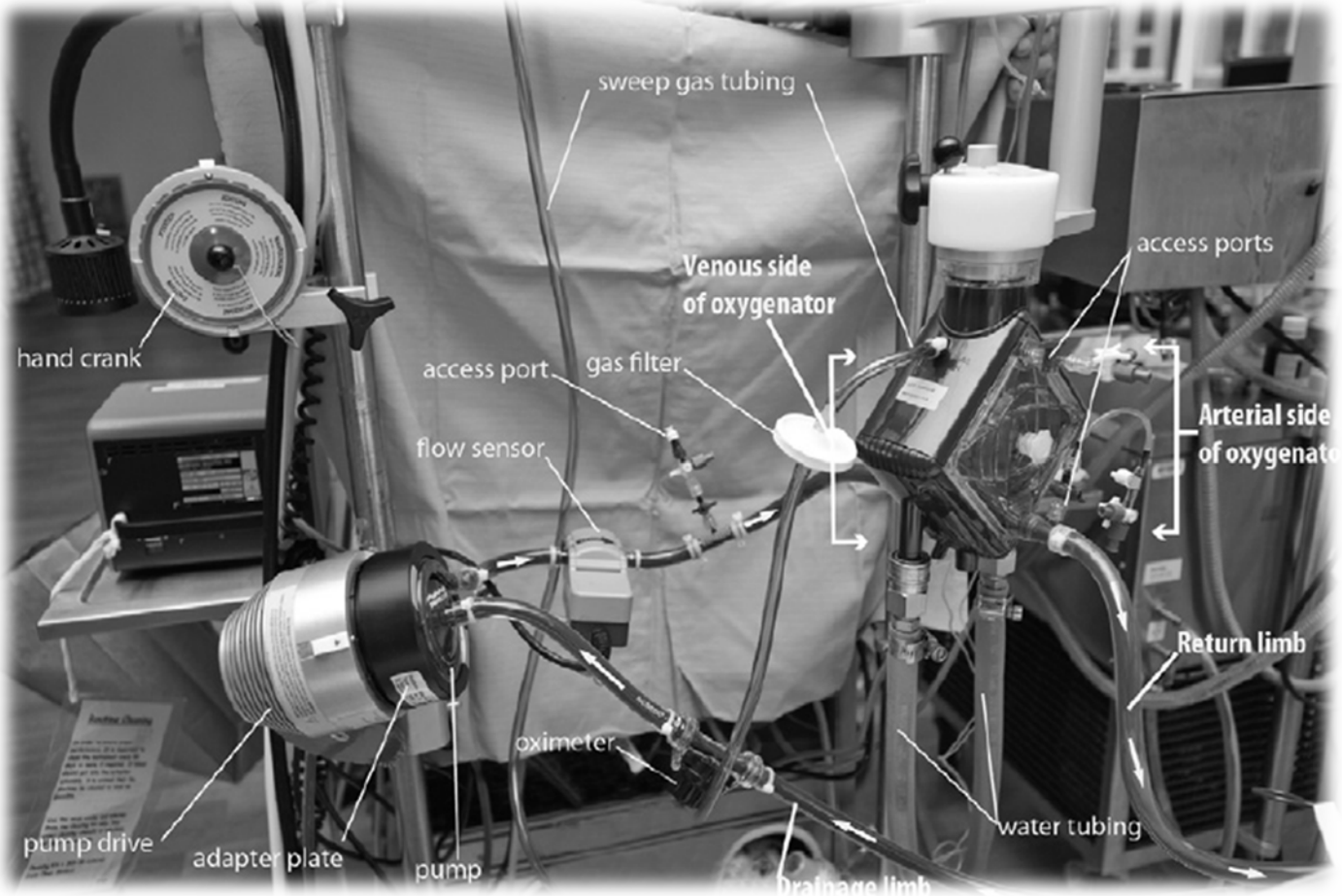


Literature Review Results for Hemodialysis

- Thrombosis of the vascular access site is an issue for dialysis patients
  - Responsible for 17-25% of patient hospitalizations
  - Costs close to $1 billion/year in the US
- Stenosis of the graft anastomosis is the main cause
- Dialysis patients are often hypercoagulable
  - Platelet factors and plasma factor abnormalities

Smits, JHM, et al., Nephrol Dial Transplant (2000) 15:1755-1760

Cardiopulmonary Bypass and ECMO



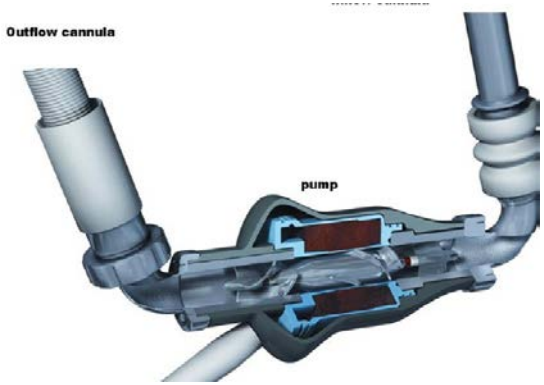
Sidebotham, D, et al. J Cardiothoracic Vasc Anesth (2012) 26(5):893-909

Search Results for Bypass and ECMO

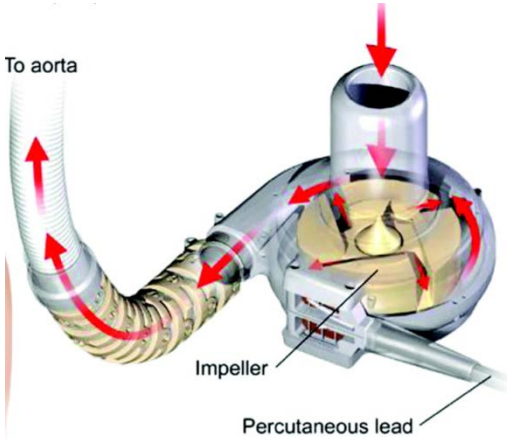
- Both MAUDE and literature searches revealed a very low amount of information on thrombus rates
  - Bleeding events were more noted
- Tubing connections are sites of disturbed or stagnant flow and can be sites of thrombus formation
- Thrombus is also often seen in the oxygenator component
- Heparin induced thrombocytopenia (HIT) is a noted occurrence in these patients

Ventricular Assist Devices (VADs)

Pulsatile flow

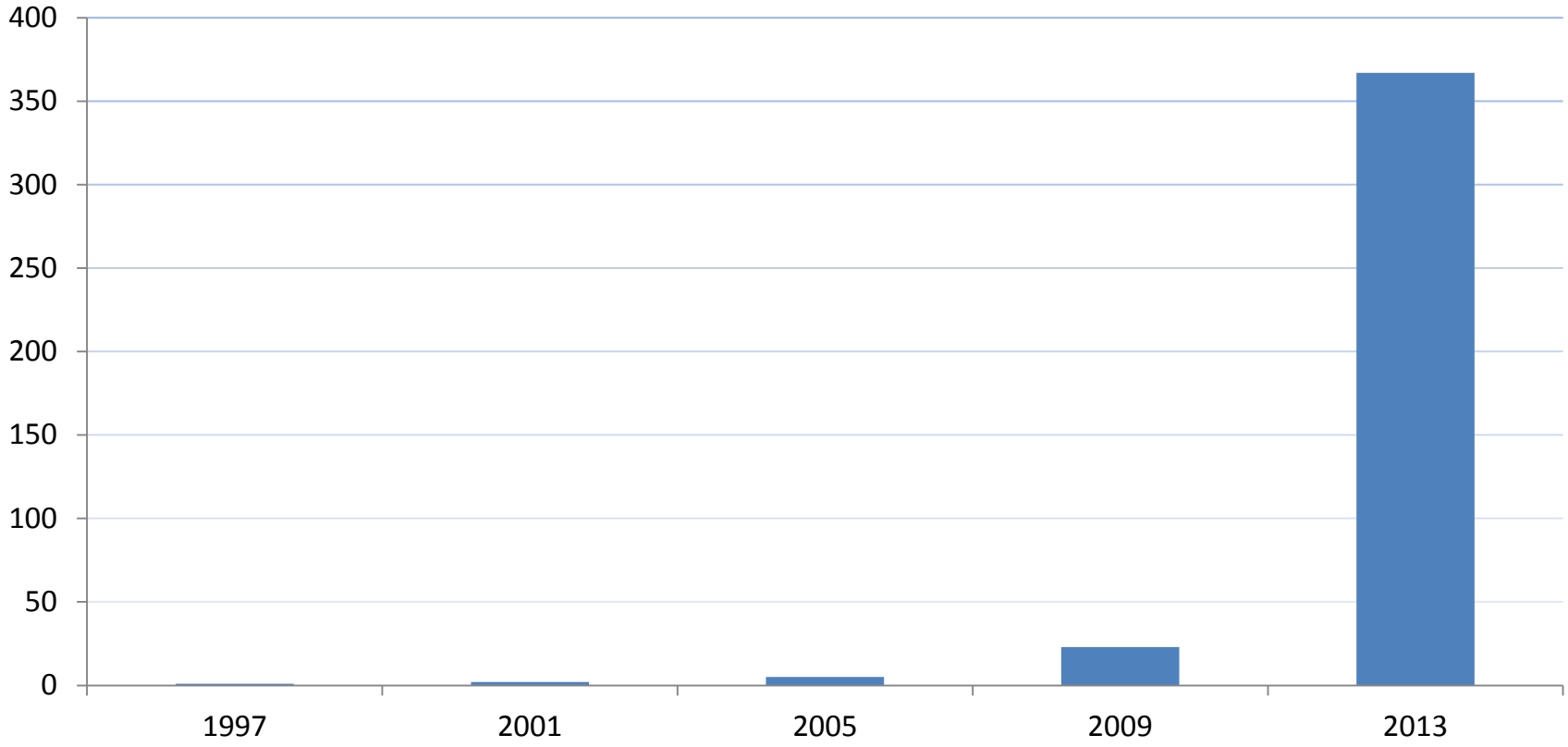


Continuous, axial flow



Continuous, centrifugal flow

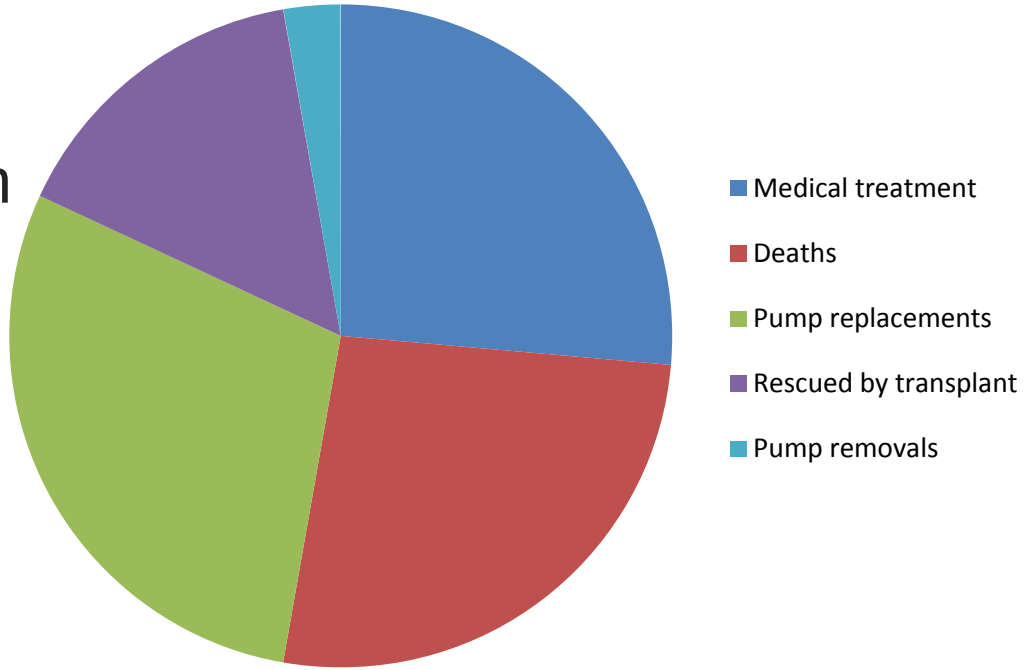
Reported Thrombus Related Adverse Events for VADs



Data from FDA's MAUDE database

Literature Review Results for VAD Thrombus

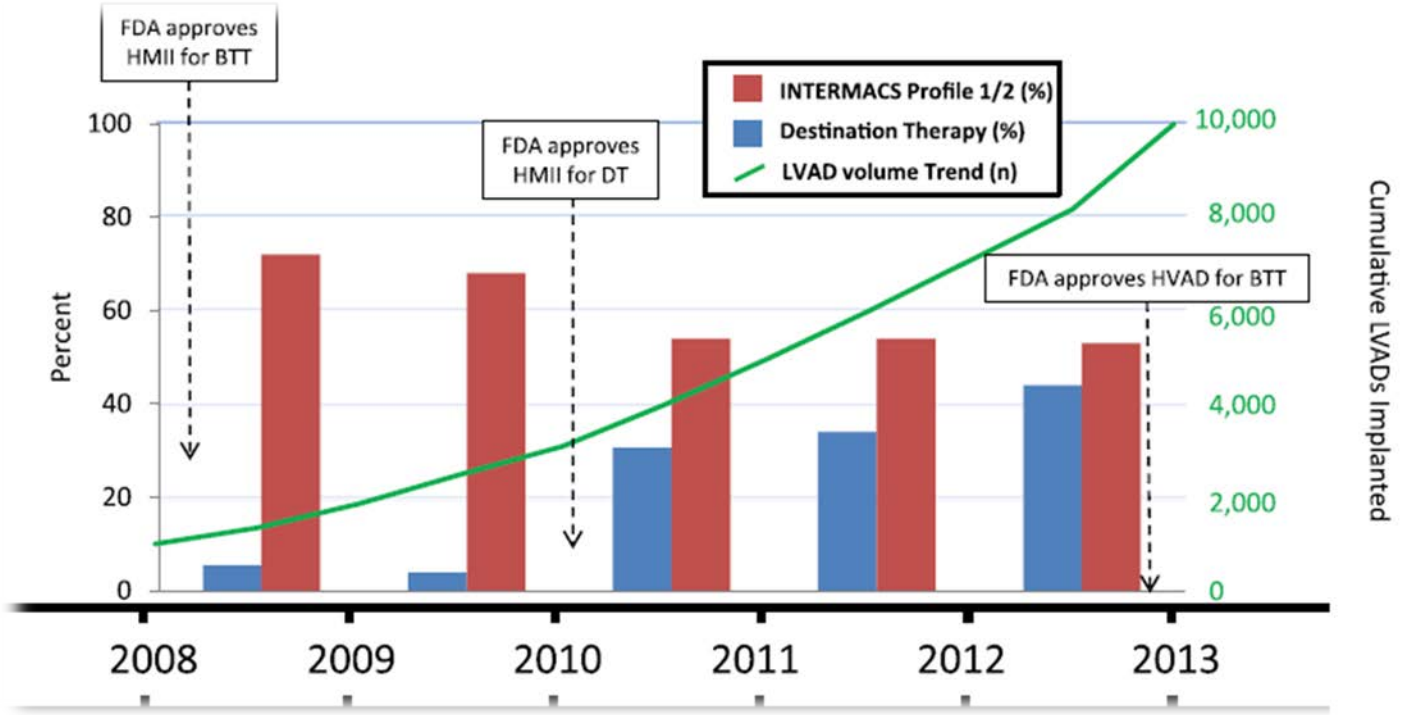
- Overall thrombus incidence with HMII 5.5%[1]
- A 6-fold increase was seen in rates of pump thrombosis in 2011 to 2012[1]
- Time to thrombotic event decreased from 18.6 months, to 2.7 months after March 2011[2]



1. Kirklin, JK et al. J Heart Lung Transplant (2014) 33(1):12-22
2. Starling, RC et al. J New Engl J Med (2014) 370:33-40

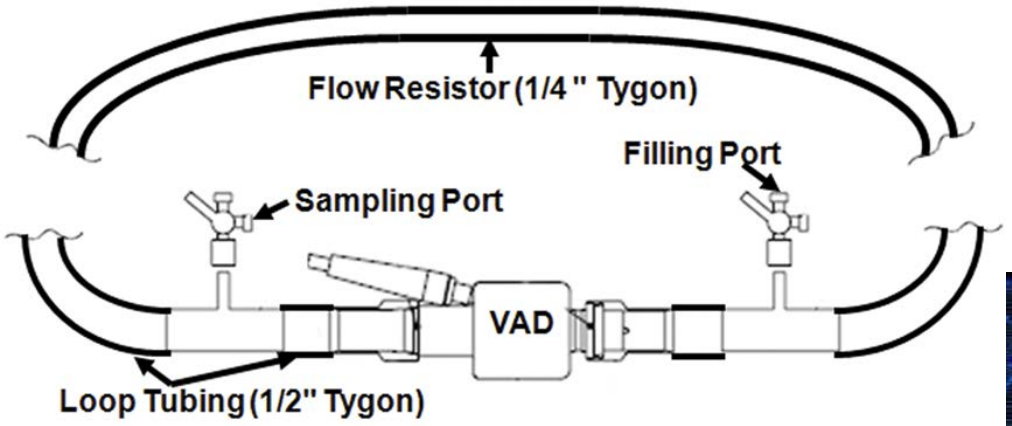
Reason for Increased Thrombus Events Unknown

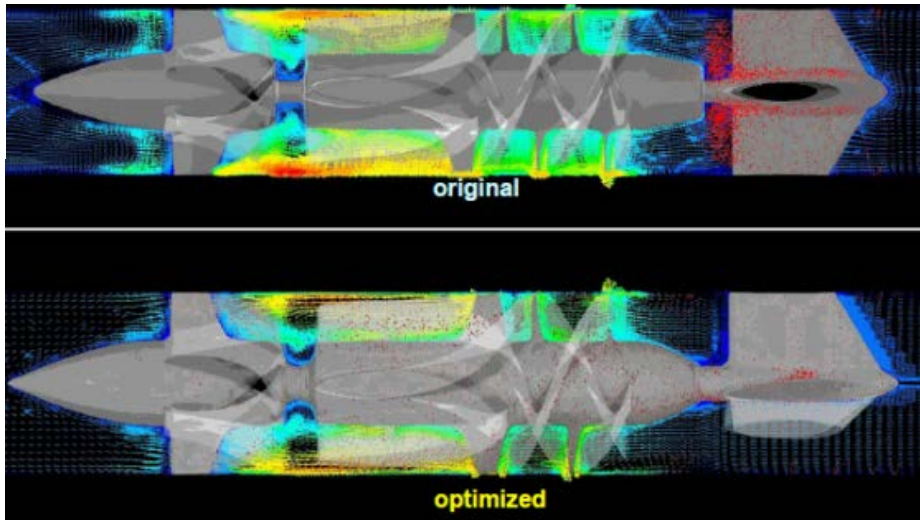
- Change in anticoagulation regimens?
- Change in inflow graft design?
- Change in patient population?



Mehra, M et al., Journal of Heart and Lung Transplantation (2014) 33(1):1-11

In Vitro and Computational Methods Used to Optimize Device Design





Girdhar, G, et al. PLoS One. 2012; 7(3):e32463

Conclusions

- Thrombus formation can lead to poor patient outcomes
- Clinical management, device design, and patient factors all impact the likelihood of thrombus formation
- *In vitro* testing may allow for device comparisons and optimization
- Adverse event reporting is low for some device types, but MAUDE database can be used for trending